

(12) UK Patent Application (19) GB (11) 2 360 845 (13) A

(43) Date of A Publication 03.10.2001

(21) Application No 0007315.5

(22) Date of Filing 27.03.2000

(71) Applicant(s)
K.U.Leuven R & D
(Incorporated in Belgium)
Groot Begijnhof, Benedenstraat 59, 3000 Leuven,
Belgium

(72) Inventor(s)
Yvo Ghoos

(74) Agent and/or Address for Service
Hugo Velge
Neaves Cottage, Neaves Lane, GLYNDEBOURNE,
East Sussex, BN8 8UA, United Kingdom

(51) INT CL⁷
A61K 51/12 , G01N 33/497

(52) UK CL (Edition S)
G1B BAA BBV
A2B BME

(56) Documents Cited
WO 97/35622 A1 WO 00/61197 A1
Chemical Abstracts Accession No: 124:134616 &
Dig. Dis. Sci. (1995), 40(10), pages 2200 - 2206.

(58) Field of Search
UK CL (Edition S) **A2B BME , G1B BAA BBV**
INT CL⁷ **A61K 51/12 , G01N 33/497**
Online: EPODOC, WPI, Japio

(54) Abstract Title
Measuring gastric emptying

(57) A method and kit for measuring gastric emptying in a test subject are characterised by using a premix of a C-13 labelled compound ,e.g. octanoic acid, and typically freeze dried egg yolk. The premix is blended with water to form a batter which is baked into a meal for ingestion by the test subject and the C-13 labelled carbon dioxide present in exhaled breath samples measured as an indicator of gastric emptying. Also claimed is a process for preparing the premix e.g. using a C-13 labelled fatty acid and freeze dried egg yolk and use of the premix to develop a medicine that alters gastrointestinal motility or transit or to investigate or formulate a diet.

Gastric emptying test-kit and method of testing gastric emptying of solid meal

FIELD OF THE INVENTION

This invention generally relates to a kit for testing gastric emptying of solids and more specifically to stable isotope labeled of medium chain fatty acid incorporated in a dry premix. More specifically it involves the improvement of the classic ^{13}C -octanoic acid egg-omelet breath test, wherein the ^{13}C -tracer had to be incorporated in a fresh test meal and the yolk phase and egg white phases had initially to be separated during baking of the omelet. In present invention it is surprisingly found that a dry premix can be prepared, comprising a mixture of the labeled egg yolk and egg white, for easy instant and in situ preparation of a test meal according to a standardized method and for reliable diagnosis of solid phase gastric emptying by monitoring the appearance of $^{13}\text{CO}_2$ in breath.

BACKGROUND OF THE INVENTION

Digestion of all foods in humans and other mammals begins in the stomach where both solid and liquid matter is mixed with gastric juices that are secreted by the stomach walls. The gastric juice is predominately hydrochloric acid, but also includes enzymes that break down food constituents so that they can be absorbed and used. The contents of the stomach are emptied into the small intestine via the pyloric sphincter, which opens and closes to release pulses of the mixed solids and liquids. The rate of such emptying is regulated by this sphincter. The rate is determined by the caloric content of the meal. The higher the caloric content, the lower the rate of discharge. In addition, the solid phase of the food must undergo reduction in particle size, which is caused by contractions of the stomach walls until a particle size of about 1 mm in diameter is attained.

A disorder in the rate of gastric emptying can result either in too rapid or in delayed emptying. When the rate is accelerated the food is "dumped" into the small intestine prematurely. When delayed, the time required to empty the stomach is excessive. Delayed gastric emptying often is encountered in diabetic patents and may be associated with abdominal pain, cramping and bloating. Even healthy people often notice subjective gastric symptoms (sinking feelings, heartburn, anorexia, etc.) in the everyday life. It has been estimated that symptoms of functional gastrointestinal disorders, those without noticeable structural, infectious, or biochemical cause, occur to some degree in nearly on quarter of all individuals who are otherwise healthy. Gastric symptoms are also caused by stress, overeating, excessive intake of

3

alcoholic drinks and intake of drugs. Additional major causes of the complaints about the digestive tracts include maldigestion, chronic gastritis, delayed gastric emptying after meals, gastric hyperacidity and peptic ulcers which bring about subjective symptoms such as abdominal swelling feelings, unpleasantness in the upper abdomen, anorexia, heartburn and belching (eructation). These functional disorders, often caused by delayed gastric emptying, require an objective, practical and efficient tests to measure gastric emptying.

In previous studies (1,2) it has been demonstrated that gastric emptying can be measured accurately by means of the ^{13}C -octanoic acid egg-omelet breath test. The ^{13}C -tracer is incorporated in a test meal, which consists of an egg omelet and three slices of bread. The test represents real advantage over the radiolabeled test meal methods to measure gastric emptying, i.e. radioscintigraphy, as it can be applied in all patients as no exposure to radioactivity is involved. Furthermore the test is simple to be performed by the patient, and several tests can be executed in the same time. By this, it represents cost-savings of instrumentation and personnel also. The use of the above non-radioactive substrates has been validated against the prior radiological methods with high correlation (1,3).

With the breath test with ^{13}C -octanoic acid "standard" egg-omelet it has been demonstrated that postgastric processing of ^{13}C -octanoic acid until $^{13}\text{CO}_2$ exhalation occurs very rapidly, with minimal intersubject variability. This is due to the very rapid absorption from the small intestine, to quick transport to the liver (no mucosal esterification, no incorporation in chylomicrons (3, 6, - 8), and to a ready and almost complete oxidation to $^{13}\text{CO}_2$ in the liver (no requirement for carnitine to cross the double mitochondrial membrane (9,10)). Therefore, gastric emptying of the meal can be considered a limiting step in $^{13}\text{CO}_2$ excretion after ingestion of a ^{13}C -octanoic acid labelled solid meal. Also an average function can be used to describe the postgastric processing of octanoic acid. Metabolism of octanoic acid remains unaltered not only in healthy volunteers but also in other circumstances, as has been shown for insulin-dependent diabetes mellitus (11) or after administration of octreotide (12)

^{13}C -octanoic had initially been selected for testing gastric emptying by a breath test since it has been shown for a long time that octanoic acid, an eight-carbon fatty acid found in dietary fats, is rapidly absorbed from the intestine and carried to the liver via the portal venous system, where it is rapidly and completely oxidised. For testing the gastric emptying of the solid food by the non-radioactive markers, ^{13}C -octanoic acid has, however, to be ingested in a freshly baked egg sandwich. The physician has thus to prepare the meal before the test administration. The nature of such a procedure makes the development of a standard solid-phase emptying protocol or procedure difficult, and hinders the commercial development of

an office-based procedure. A prepared and pre-packaged test kit would have the advantage of storage at room temperature, instant availability and ease of transportation to the place of an experimental set up for in situ diagnosis. However, this development was hindered by the fact that as a rule the egg yolk homogenized with ^{13}C -octanoic acid had to be baked separately from the egg white to ensure a firm retention of the label in the solid phase of the meal (1).

To overcome the problems mentioned above with the current ^{13}C -octanoic acid breath test and to avoid the use of radioactive tracer, Klein Peter D, 1989 (4) proposed the use of single cell organisms as markers for solid-phase meals. The intrinsically labeled single cell marker organisms, proteins, lipids or carbohydrates were incorporated into a baked product that is ingested by the patient. The product containing the marker organisms was a biscuit having an edible photosynthetic alga therein, such as *Spirulina platensis*. The alga had to be photosynthetic and had to be grown in an atmosphere of about 99% $^{13}\text{CO}_2$, so that as a consequence of the photosynthetic process all carbon atoms contained in the alga would be ^{13}C . The labeled single cell marker organisms were then mixed in a batter with proteins, lipids or carbohydrates and were baked into a biscuit for ingestion by the patient. Although this technique could overcome the disadvantages of inconvenience and standardization related to fresh meal preparation and to egg white / egg yolk separation in the classic egg-omelet breath test, it still requires a controllable alga culture process in a photosynthetic reaction tank with nutrient solutions and $^{13}\text{CO}_2$ gas input. The inconsistency of such life process may affect the reliability of the final test product.

Furthermore, growing photosynthetic alga in an air atmosphere enriched with $^{13}\text{CO}_2$ atmosphere will result in the incorporation ^{13}C atom in a variety of functional and structural proteins, fat and carbohydrate macromolecules. Because of their varied chemistry and physical form the rate and extent to which the different types of nutrients are digested in and absorbed from the small intestine and the metabolism of the different fatty acids, amino acids or sugars will vary.

The $^{13}\text{CO}_2$ breath test is an indirect measurement of gastric emptying since the $^{13}\text{CO}_2$ appearance curve reflects the sum influence of gastric emptying, digestion, absorption and metabolism. The availability, absorption and metabolic processing of a labeled compound must thus be fast and reproducible to obtain only gastric emptying as rate limiting step. This is obtained with octanoic acid in particular and likely with other medium chain fatty acids, since they are absorbed by the small intestine and are rapidly transported to the liver bound to serum albumin for free entering in the mitochondria and fast oxidation to CO_2 . These features make medium chain fatty acids, on condition that they are not freely available in the stomach, suitable for measuring gastric emptying. The proteins of single cell organisms, however will

4

undergo a complex series of degradative processes which are elucidated by the hydrolytic enzymes originating from the stomach, pancreas and the brush border of the small intestine. Pancreatic digestion plays a critical role in the overall protein assimilation. Since it has been previously been demonstrated by a ^{13}C -labeled protein meal ingestion and $^{13}\text{CO}_2$ exhalation, that protein assimilation and not the metabolism of the amino acids is the rate limiting step, ^{13}C -labeled protein test can be considered a promising test for the evaluation of the digestibility of protein and the evaluation and the follow up of exocrine pancreatic function (13) but not for measurement of gastric emptying, especially not for patients with malabsorption symptoms. For instance with ^{13}C egg white, generally considered to be highly digestible, there exists in a breath test a very good correlation between the $^{13}\text{CO}_2$ production and the pancreatic trypsin output in the duodenum (13). Nevertheless, not all egg white proteins are well absorbed. Some undergo additional fermentation in the colon, which results in CO_2 release, origination from bacterial metabolism (20).

There is thus a need for a safe, practical, accurate and ease to standardize test to diagnosis of gastric emptying of solids. This invention provides these features by improvement the classic ^{13}C -octanoic acid egg-omelet test (in use since the early nineties) to a test kit with a dry ^{13}C -octanoic acid premix. This was a challenge since in the classic egg-omelet test ^{13}C octanoic acid enriched yolk and egg white has to baked separately to avoid that ^{13}C is released and absorbed in the stomach. In the kit of present invention, both fractions of the egg, i.e. egg white and labeled yolk, are in the same powder mix, without losing the diagnostic properties.

SUMMARY OF THE INVENTION

For the classic octanoic acid breath test, ^{13}C ,tracer is incorporated in a test meal, which consists of an egg omelet and three slices of bread. This meal has to be prepared just before the test starts. By consequence the patients have to come to the laboratory unit, where the test meal is served. During 4 hours the patient stays at the laboratory and is asked to blow in a tube every 15 minutes.

Present invention involves the development of a test-kit that can be send as such to other hospitals, and even the patient can take the test-kit at home where the test can be executed at time, convenient for the patient. Until now this was not possible for the ^{13}C ,octanoic acid breath test, since the present test meal, i.e. egg omelet had to be prepared freshly by homogenizing of ^{13}C -octanoic acid in yolk and baking it separately from the egg white just before the test started (1,2, 3, 5, 12 – 19)

5
By this invention we present for the first time the test meal as prepackaged food in such a way that a test-kit can be composed, which allows the measurement of gastric emptying out of the hospital with results, equally good as the “standard” egg-omelet meal.

The present meal, containing the ^{13}C , octanoic acid, is a powder, to which water is added to obtain a batter. The batter allows to bake a pancake, which upon digestion is equally reliable as the omelet to measure gastric emptying by $^{13}\text{CO}_2$ breath test. The pancake-powder has been prepared following the hygienic procedures, common in food industries. It is packed water-free, kept under nitrogen and wrapped in aluminum foil. The test-kit is further composed of test tubes and all information to execute the test properly.

Advantages are double: *first*, the patients are not obliged to come to the hospital; upon instructions the test can even be executed at home. *Second*, it is guaranteed that the powder is kept fresh for more than one year.

In the present study we prove that the novel test meal (pancake-powder) is equally good as the omelet meal to measure gastric emptying by $^{13}\text{CO}_2$ breath test.

EXAMPLES

Example 1 Production of the pre-packed test kit

Test meal:

The pancake-powder is composed per unit pancake in the following way:

In laboratory conditions, per 8.6 g egg yolk 100 microliter ^{13}C , octanoic acid is added and mixed for homogeneous distribution of the tracer in the yolk-material, consequently this is lyophilized. Consequently this is mixed with 3.75 g lyophilized egg white, 17 g wheat flour and 3 g milk powder. A total weight of the powder is 32.35 g; it represents 179.1 kcal. The premix is used in this amounts to prepare one pancake. The same premix has, however, also been prepared on larger scale by Ovofood, Herk-de-Stad, Belgium. An aluminum sachet with premix in the amount to prepare one pancake makes part of the test kit.

To make the pancake 32.35 g of the powder premix is suspended in 70 ml of water, and the batter is baked in the pan by addition of 3 g fat. The pancake is served with an additional amount of 5 g (beet)sugar as sweetener. Total caloric intake is 225.1 kcal.

Example 2 Measuring gastric emptying of the solid phase with the pre-packed test kit

Subjects:

There are four groups of normal individuals involved in the comparative study:

group A: the individuals, as described in the publication (1)

group B: the individuals as described in ref 2.

group C: sixteen normal individuals took a pancake, of which the powder has been prepared by the laboratory personnel.

group D: eight normal individuals took a pancake, of which the premix powder has been prepared in an industrial manner by Ovofood, Herk-de-Stad, Belgium.

Every patient receives 1 plastic straw and 18 tubes with screw cap from the test kit. The test is preferably executed in the morning (at starvation). The patients stay in rest during the test, although a slow walk is permitted. They stay in upright position the first two hours of the test; after that time more conformable position may be adopted, but never they are allowed to lie down.

To provide a breath sample, the patients keep the straw at the bottom of the tube, they inhale deeply and expirate 5 seconds through the straw. The tube is immediately closed thereafter.

The test is performed as follows:

Before ingestion of the pancake the patients blow in the first vial and half a minute thereafter in vial 2. The pancake is eaten within 10 minutes. As drink (150-ml) only water, coffee or tea is allowed. Coffee or tea can be creamed and/or sweetened, but not with cane sugar. A soft drink or fruit juice is not allowed. During the test, small quantities (20 ml) of drinks can be taken, just to cut thirst. 15 minutes after the end of the meal the patients blow in the next tube. 30 minutes after the end of the meal the patients blow into tube 4. Every 15 minutes thereafter the patients blow in the next tube, up to 4 hours (240 min). The test end after 4 hours.

Analysis of the tubes

^{13}C contents in breath is determined by on line gas chromatographic purification-isotope ratio mass spectrometry (ABCA; Europe Scientific). The δ value given by the isotope ratio mass spectrometry are converted to percentage ^{13}C recovery of the initial amount administered per hour (% dose $^{13}\text{C}/\text{h}$) according to calculations described in detail by Ghooos et al (5)

Statistics:

Analysis of variance on average $t_{1/2}$ - value is done (ANOVA-test). The level of significance is set at $p < 0.05$. The program used was SAS/STAT release 6.03 Edition 1 (SAS institute Inc. Raleigh, NC)

Results:

In the following table the values of test results are shown, following the four groups

Table I:

	group A	group B	group C	group D
n =	42	10	16	8
t _{1/2} (mean)	72	68	80	71
sd	22	27	21	18
+ 2 sd	118	122	122	107
- 2 sd	20	14	38	35

Statistical evaluation:

No significance level was reached.

DISCUSSION

By comparative studies it has been demonstrated that there is no statistical difference when the omelet meal is replaced by the pancake to measure gastric emptying by $^{13}\text{CO}_2$ breath test. The pancake meal shows great advantages over the omelet meal. It is no longer necessary that the patient presents to the hospital to execute the breath test. Even the test can be done at home, when the patient is properly instructed. The breath samples have to be sent to the analytical unit, and the test results are sent to the medical doctor, who informs the patient. By this method it will be easier in the future to study the influence of pharmacological modulation of gastric emptying as the test meal is uniform for all individuals involved in the study, and as the test can be executed over the world, wherever wanted. As the powder keeps fresh over a long time, clinical investigations and pharmacological effects can be planned over a widespread period. This meal enables to present the $^{13}\text{CO}_2$ breath test for gastric emptying as a test-kit, which makes the whole procedure uniform and repeatable for all persons, to whom the test can be applied.

In conclusion: The proposed method, which gives results similar as the omelet method, can be considered very reliable to measure gastric emptying of solids, as the egg omelet method provides an excellent correlation between gastric half-emptying time ($r=0.98$) and log phase ($r=0.85$), determined via $^{13}\text{CO}_2$ breath test and radioscintigraphy, which is classically considered to be a reference method (3). The pancake method to study gastric emptying by means of the $^{13}\text{CO}_2$ breath test offers great advantage over other test meals. It is foreseen that the proposed pancake test meal will have great acceptance in clinical practice and research.

Fields of applications: The presented test can be applied in all categories of the population, children, adults, pregnant women, elderly people.

in clinical diagnostic context:

Measuring gastric emptying in children, adults and elderly people in the hospital. The test can be sent to other hospitals as a test-kit, and can even be taken at home to have the test done by the patient at the time, which is the most convenient for him(her).

in research context:

- in clinical research: the test can be considered reference method to demonstrate gastric emptying in different pathological conditions. To the presented test meal (pancake powder) other tracer molecules can be added to study gastrointestinal functions, other than gastric emptying, e.g. assimilation of carbohydrates, lipids, proteins, oro-cecal transit, bacterial overgrowth or/and fermentation processes in the colon.
- in pharmaceutical research: the test can be taken as reference method for testing and developing drugs, affecting gastrointestinal motility and transit.
- in nutritional research: the test can also be taken as reference method to demonstrate gastric emptying of food formula.

References

- 1) *Ghoos YF, Maes BD, Geypens BJ, Mys G, Hiele MI, Rutgeerts PJ, Vantrappen G*
Measurement of gastric emptying rate of solids by means of a carbon-labeled octanoic acid breath test. Gastroenterology 1993 Jun;104(6):1640-7
- 2) *Maes B.D., Ghoos Y.F., Geypens B.J., Mys G., Hiele M.I., Rutgeerts P.J., Vantrappen G. :*
Combined carbon 13-glycine/carbon-14-octanoic acid breath test to monitor gastric emptying rates of liquids and solids. J. Nucl. Med. 35: 824-831, 1994.
- 3) *Maes B., Mys G., Geypens B., Evenepoel P., Ghoos Y., Rutgeerts P.: Gastric emptying flow curves separated from carbon-labeled octanoic acid breath test results. Am. J. Physiol., 275, G169 - G175, 1998*
- 4) *Klein Peter D., Measurement of gastric emptying, US5707602, CA2239018, EP0889739, WO9735622*
- 5) *Ghoos Y, Geypens B., Maes B. et al. Breath tests in gastric emptying and transit studies: technical aspects of 13CO2-breath tests. In: Janssens J, ed. Progress in understanding and management of gastro-intestinal motility disorders. K.U.Leuven: Belgium, 1993: 169 – 80.*
- 6) *Iber F. Relative rates of metabolism of MCT, LCT and ethanol in man. In: Mittelkettige in der Diät, edited by H. Kaunitz, Lang and W. Fekl. Berlin: Z. Ernährungswiss, 1974, vol. 17, p 9-16.*

- 7) Mishkin, S. L. Stein, Z. Gatmaitan, and I. M. Arias. *The binding of fatty acids to cytoplasmatic proteins: binding to Z protein in liver and other tissies of rat.* *Biochem. Biophys. Res. Commun.* 83:479 – 485, 1978.
- 8) Ockner, R. K., J. A. Manning, R.B.Poppenhausen and W.K. Ho A binding protein for fatty acids in cytosol of intestinal mucosa, liver, myocardium and other tissues. *Science* 177: 56 – 58, 1972.
- 9) Bremer J. Carnitine and its role in fatty acid metabolism. *Trends Biochem. Sci.* 2: 207 – 209, 1980.
- 10) Scheig, R. Hepatic metabolism of medium chain fatty acids. In: *Medium Chain Triglycerides*, edited by J.R. Senior. Philadelphia, PA: Univeristy of Pennsyivania, 1968, p. 39 – 49.
- 11) Maes, B.D. *Measurement of gastric emptying using dynamic breath analysis*, edited by B. Maes. Leuven, Belgium: Acco 1994.
- 12) Maes, B.D., Y. F. Ghooos, B.J. Geypens, M.I. Hiele, and P.J. Rutgeerts. *Inflence of octreotide on gastric emptying of solids and liquids in normal healthy volunteers.* *Aliment. Pharmacol. Ther.* 9: 11-18, 1995.
- 13) Evenepoel P., M Hielle, Geypens B., Geboes K.P., Rutgeerts P. and Ghooos Y. *¹³C-egg white breath test: a non-invaisve test of pancratic trypsin activity in the small intestine.* *Gut*, January 2000, Vol 46, No 1, p 52-57.
- 14) Van Den Driessche M, Peeters K, Marien P, Ghooos Y, Devlieger H, Veereman-Wauters G *Gastric emptying in formula-fed and breast-fed infants measured with the ¹³C-octanoic acid breath test.* *J Pediatr Gastroenterol Nutr.* 1999 Jul;29(1):46-51.
- 15) Maes BD, Hiele MI, Geypens BJ, Ghooos YF, Rutgeerts PJ *Gastric emptying of the liquid, solid and oil phase of a meal in normal volunteers and patients with Billroth II gastrojejunosomy.* *Eur J Clin Invest* 1998 Mar;28(3):197-204
- 16) Maes BD, Geypens BJ, Ghooos YF, Hiele MI, Rutgeerts PJ *¹³C-Octanoic acid breath test for gastric emptying rate of solids.* *Gastroenterology* 1998 Apr;114(4):856-9
- 17) Pfaffenbach B, Wegener M, Adamek RJ, Wissuwa H, Schaffstein J, Aygen S, Hennemann O. *Non-invasive ¹³C octanoic acid breath test for measuring stomach emptying of a solid test meal--correlation with scintigraphy in diabetic patients and reproducibility in healthy probands.* *Z Gastroenterol* 1995 Mar;33(3):141-5
- 18) Maes BD, Ghooos YF, Rutgeerts PJ, Hiele MI, Geypens B, Vantrappen G *[*C]octanoic acid breath test to measure gastric emptying rate of solids.* *Dig Dis Sci* 1994 Dec;39(12 Suppl):104S-106S

19) Maes BD, Hiele MI, Geypens BJ, Rutgeerts PJ, Ghoo YF, Vantrappen G

Pharmacological modulation of gastric emptying rate of solids as measured by the carbon labelled octanoic acid breath test: influence of erythromycin and propantheline.

Gut 1994 Mar;35(3):333-7

20) Evenepoel P., Claus D., Geypens B., Hiele M., Geboes K., Rutgeerts P and Ghoo Y.

Amount and fate of egg protein escaping assimilation in the small intestine of humans.

AM. J. Physiol. 277 G935- G943, 1999

CLAIMS

1. A method of diagnosing gastric emptying of the solid phase in a subject, which comprises the steps of mixing water with ^{13}C labeled molecules in said a powdered premix, baking said the resulting batter into a solid meal, ingesting said solid meal and measuring $^{13}\text{CO}_2$ in breath samples.
2. The method in accordance with Claim 1 wherein the ^{13}C labeled substrate is a fatty acid.
3. The method in accordance with Claim 1 wherein the ^{13}C labeled substrate is a medium chain fatty acid.
4. The method in accordance with Claim 1 wherein the ^{13}C fatty acid is an octanoic acid.
5. A test kit for carrying out the method of any preceding claims comprising a prepackaged premix.
6. The test kit of claim 5 further comprising tubes with cap and comprising at least 1 straw for blowing.
7. A process for producing said premix of any of the claims 1 to 6 wherein the ^{13}C labeled fraction is obtainable from freeze dried egg yolk.
8. A process for producing said premix of any of the claims 1 to 6 wherein the ^{13}C labeled fraction is obtainable from spray dried egg yolk.
9. The process of the claims 7 or 8, wherein the powdered premix comprises a mixture of said labeled egg yolk with powdered egg white.
10. The process of the claims 7 or 8, wherein the powdered premix comprises a mixture of said labeled egg yolk with powdered egg white, wheat flour and milk powder in suitable amounts to prepare a solid meal.
11. Use of the premix of any of the claims 1 to 10 to test or develop a medicine that alter gastrointestinal motility or gastrointestinal transit.
12. Use of the premix of any of the claims 1 to 10 to investigate or formulate a diet.



INVESTOR IN PEOPLE

Application No: GB 0007315.5
Claims searched: 1 - 10

Examiner: Michael R. Wendt
Date of search: 21 February 2001

Patents Act 1977 Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:
UK Cl (Ed.S): A2B (BME); G1B (BAA, BBV)
Int Cl (Ed.7): A61K 51/12; G01N 33/497
Other: Online: EPODOC, WPI, Japio, CAS

Documents considered to be relevant:

Category	Identity of document and relevant passage	Relevant to claims
A,E	WO 00/61197 A1 (MASSTRACE) e.g. see page 22 lines 16 etc;	1
A	WO 97/35622 A1 (MERETEK) e.g. see page 4 lines 10 etc; Claims.	1
A	Chemical Abstracts Accession No: 124 : 134616 & Dig. Dis. Science (1995), 40(10), pages 2200 - 6. See Abstract.	1

X Document indicating lack of novelty or inventive step
Y Document indicating lack of inventive step if combined with one or more other documents of same category.
& Member of the same patent family

A Document indicating technological background and/or state of the art.
P Document published on or after the declared priority date but before the filing date of this invention.
E Patent document published on or after, but with priority date earlier than, the filing date of this application.